Citation:

Lucas A, Morley R, Hudson GJ, Bamford MF, Boon A, Crowle P, Dossetor JF, Pearse R. Early sodium intake and later blood pressure in preterm infants. Ar*ch Dis Child.* 1988 Jun; 63(6): 656-657.

PubMed ID: 3389898

Study Design:

Randomized trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEGATIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To test whether blood pressure at 18 months post-term in pre-term infants differed between those assigned randomly, for the early postpartum weeks, to diets differing significantly in sodium content.

Inclusion Criteria:

Inclusion criteria are described elsewhere, in Lucas A, Gore SM, Cole TJ, et al. A multicentre trial on the feeding of low birthweight infants: Effects of diet on early growth. *Arch Dis Child.* 1984: 59: 722-730. (See Reviewer Comments.)

Exclusion Criteria:

Exclusion criteria are described elsewhere, in Lucas A, Gore SM, Cole TJ et al. A multicentre trial on the feeding of low birthweight infants: Effects of diet on early growth. *Arch Dis Child.* 1984: 59: 722-730. (See Reviewer Comments.)

Description of Study Protocol:

Recruitment

Recruitment is described elsewhere, in Lucas A, Gore SM, Cole TJ et al. A multicentre trial on the feeding of low birthweight infants: Effects of diet on early growth. *Arch Dis Child.* 1984: 59: 722-730.

Design

Randomized trial.

Intervention

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- The trials originally were designed to measure differences in feedings of donor breast milk, standard formula and pre-term formula with or without expressed breast milk. As there was no difference in blood pressure between infants fed donor breast milk or standard formula, data were from those trials were combined.
- Two studies compared blood pressure and type of milk consumed:
  - Study 1: Infants who were fed donor milk or standard formula vs. pre-term formula as sole diet
  - Study 2: Infants who were fed donor milk or standard formula vs. pre-term formula in conjunction with expressed maternal breast milk (mean = 46% of feed volume)
- Infants remained on the assigned diet until they reached 2,000g or were discharged.

Mean (SE) Na (mmol per L) Content of Milks		
A Type of Milk	**Na Content (mmol per L)**	**Comments**
Banked donor breast milk	7.2(0.1)	Averaged over hospital stay
Standard formula	8.3	
Pre-term formula	19.6	
Expressed breast milk	11.0(0.15)	Average of 1,776 24-hour milk collections

Pre-term formula (Osterprem) and Standard formula (Osterfeed) were from Farley Health Products Ltd.

Statistical Analysis

- Descriptive statistics (means and SE) were presented
- P-values were reported, but method of analysis was not.

Data Collection Summary:

Timing of Measurements

Arterial blood pressure was taken at 18 months (corrected for pre-term birth) of age.

Dependent Variables

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were recorded with a conventional sphygmomanometer using a cuff with a size appropriate to the infant's weight and age.

Independent Variables

Type of feeding:

- Banked breast milk/term formula
- Pre-term formula (high Na)
- Pre-term formula (high Na) and expressed maternal breast milk
- Banked breast milk/term formula and expressed maternal milk.

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Control Variables

- Weeks of gestation
- Birth weight
- Sex
- Median days on assigned diet.

Description of Actual Data Sample:

- *Initial N:*
  - Total of 347 pre-term male and female infants
  - Number in each arm of the study:
    - Study 1: Supplements were sole diet
      - Donor milk or standard formula: N=56
      - Pre-term formula: N=54
    - Study 2: Supplements added to expressed breast milk intake
      - Donor milk or standard formula: N=116
      - Pre-term formula: N=121
- *Attrition (final N):* Total of 347 infants were included in analysis
- *Age:* Pre-term infants from birth to 18 months (corrected for pre-term birth)
- Anthropometrics: Birth weight is shown in table
- Location: England.

Summary of Results:

Early Sodium Intake and Blood Pressure at 18 Months in Pre-term Infants

Characteristic	Study 1 Banked Breast Milk/term Formula	Study 2 Pre-term Formula (High Na)	Study 3 Banked Breast Milk/term Formula + Expressed Maternal Breast Milk	Study 4 Pre-term Formula (High Na) + Expressed Maternal Breast Milk
Number (male/female)	56(26/30)	54(24/30)	116(61/55)	121(67/54)
Mean (SE weeks of gestation	31(0.4)	31(0.3)	31(0.3)	31(0.2)
Mean (SE) birth weight (g)	1,373(40)	1,408(36)	1,400(28)	1,405(25)
Median days on assigned diet (quartiles)	37(22.50)	27(18.38	30(21.50)	27(18.39)

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Mean (SE) blood pressure (mmHg)				
Systolic	97.7(1.3)	96.6(1,3)	97.8(0.9)	96.6(0.9)
Diastolic	65.4(1.1)	66.1(0.8)	65.8(0.7)	65.5(0.7)

Other Key Findings

- Infants on the pre-term formula took longer to attain full enteral feeds, but spent less time in hospital and therefore on the assigned diet
- No group differences were found in SBP or DBP at 18 months in either study
- No differences were found in a subgroup of 87 infants under 1,200g birth weight, who spent a longer period (mean 60 days) on the diet allocated
- A small trend to higher BP in boys than in girls [SBP, 97.9 (0.7) vs. 96.2 (0.7) mmHg and DBP, 66.4 (0.6) vs. 64.9 (0.6) mmHg] was not significant.

Author Conclusion:

Data obtained thus far to 18 months do not support the view that high-sodium pre-term formulas cause a later rise of blood pressure, or the more general thesis that a high salt intake in early infancy has an adverse imprinting.

Reviewer Comments:

Inclusion and Exclusion criteria are described in: Lucas A, Gore SM, Cole TJ, et al. A multicentre trial on the feeding of low birthweight infants: Effects of diet on early growth.Arch Dis Child. 1984: 59: 722-730, as follows:

- *Inclusion criteria: Infants less than 1,850g admitted to the special care baby unit at any one of five centers (Campbridge, Ipswich, Kings Lynn, Norwich or Sheffield), regardless of whether they are well or ill*
- *Exclusion criteria:*
  - *Lack of parental consent after full explanation*
  - *Severe congenital abnormality known to influence growth or neurological development*
- *Strengths:*
  - *The study included an adequate number of subjects, with a large sample size*
  - *The length of exposure to the various treatments was included in analysis*
- *Limitations:*
  - *To find out about recruitment and selection of subjects, need to go back to a previous paper*
  - *No discussion of compliance or any measure that the estimated Na intake was correct*
  - *Unclear if BP measurements were done by a person blinded to treatment*
  - *Lack of information on how many BP measures were taken*
  - *Lack of information as to which Korotkoff sounds were used for measures of BP*
  - *Subjects included all pre-term infants, both sick and healthy*
  - *Power calculations for the study were based on the number of infants needed to detect a specific amount of weight gain, and not on hypothesized differences in BP*
  - *No information on withdrawals of study subjects provided*
  - *Financial support from manufacturer of formula fed in study*
  - *Statistical analyses not fully described*

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- *Per authors, the infant diets used differed in other respects than their sodium content, and these differences may have increases differences in renal solute loading; 18 months is early to examine a dietary effect on BP.*

Comments

- *The paper explains why the Na content of pre-term formula is high: "Sodium content in pre-term infant formulas is usually substantially higher than in standard formulas or breast milk. These special formulas have been designed to meet high sodium requirements of pre-term neonates; however, this requirement falls post-natally and there is a concern that many babies may receive unnecessarily high Na intakes during their later weeks in hospital."*
- *Blood pressure measurements at 18 months seem to indicate that the infants adapted to their early levels of Na intake.*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes
1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	No
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	No
2.2.	Were criteria applied equally to all study groups?	???

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2.3.	Were health, demographics, and other characteristics of subjects described?	No
2.4.	Were the subjects/patients a representative sample of the relevant population?	???
3.	**Were study groups comparable?**	No
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	No
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	???
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	No
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	No
4.1.	Were follow-up methods described and the same for all groups?	???
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	No
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	???
4.4.	Were reasons for withdrawals similar across groups?	???
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	No
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	No
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	No

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5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	No
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	No
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	???
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	???
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	No
6.6.	Were extra or unplanned treatments described?	No
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	No
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	???
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	???
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	???
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	No

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8.1.	Were statistical analyses adequately described and the results reported appropriately?	No
8.2.	Were correct statistical tests used and assumptions of test not violated?	???
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	No
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	No
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	No
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**	No
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	???
10.	**Is bias due to study's funding or sponsorship unlikely?**	No
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	No

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